UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,320	12/13/2004	Yasushi Nakada	262891US0PCT	3886

22850 7590 05/25/2007

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
SHIAO, REI TSANG	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
05/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,320	NAKADA ET AL.	
	Examiner	Art Unit	
	Rei-tsang Shiao, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/19/06, 1/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application claims benefit of the foreign application:

JAPAN 2002-173483 with a filing date 06/14/2002. However, an English-translated Version of the certified copy of the foreign priority document has not been filed, the instant foreign priority has not been granted.

2. Claims 1-8 are pending in the application.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements, filed on July 19, 2006, and January 12, 2005 have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

Responses to Election/Restriction

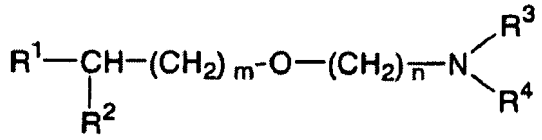
4. Applicant's election with traverse of election of Group III 1-8, in part, in the reply filed on April 20, 2007 is acknowledged. As a single disclosed species, applicants elected compound A3, i.e., 1-[3-(2-(1-benzothiophen-5-yl) ethoxy)-propyl]-3-azetidinol, and compound B1, i.e., Donepezil, is also acknowledged. The traversal is on the grounds that restriction is only proper if the claims of the restricted groups are independent or patentably distinct and there would be a serious burden placed on the Examiner if restriction is not required, and MPEP §803 is cited.

This is found persuasive, in part, and the reasons are given *infra*.

Claims 1-8 are pending in the application. The scope of the invention

of the elected subject matter is as follows.

Claims 1-8, in part, drawn to a pharmaceutical composition comprising ingredients (A), wherein the ingredients (A) is compounds of the formula, i.e.,



, wherein R^1 is a benzothienyl which may be substituted with a group selected from a halogen atom, an alkyl group and a phenyl group; R^2 is a hydrogen atom; R^3 and R^4 is an alkyl group, or R^3 and R^4 taken conjointly with the nitrogen atom to which R^3 and R^4 are linked form an azetidine ring thereof; m is 1 ; and n is 2 to 3; or a salt thereof. and the ingredients (B) is selected from the group consisting of Donepezil (compound B1),Tacrine (compound B2), Rivastigmine, Galanthamine, Zanapezil and Phenserine thereof, and their processes of making.

The claims 1-8 herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art, see Schimada et al. CAS:127:362624. Schimada et al. disclose similar benzothienyl compounds as the instant invention. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Furthermore, even if unity of invention under 37 CFR 1.475(a) is not lacking, which it is lacking, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following

combinations:

(1) A product and a process specially adapted for the manufacture of said product', or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

However, it is noted that unity of invention is considered lacking under 37 CFR 1.475(a) and (b). Therefore, since the claims are drawn to more than a product, and according to 37 CFR 1.475 (e)

the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims lack unity of invention and should be limited to only a product, or a process for the preparation, or a use of the said product. In the instant case, Groups I-IV are drawn to various products, processes of making, and the final products do not contain a common technical feature or structure, and do not define a contribution over the prior art, i.e., similar benzothienyl compounds. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

Claims 1-8, in part, embraced in above elected subject matter, are prosecuted in

the case. Claims 1-8, in part, not embraced in above elected subject matter, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the ingredient (B) represents Donepezil (compound B1) or Tacrine (compound B2), does not reasonably provide enablement for the ingredient (B) represents a compound without limitation, see claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Dependent claims 2-8 are also rejected along with claim 1 under 35 U.S.C. 112, first paragraph.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a pharmaceutical composition comprising an ingredient (B) without limitation, see claim 1.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that a physostigmine compound of formula as acetylcholine esterase inhibitors, see Glamkowski et al. US 5,081,117.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the exemplary compounds on pages 17-18 of the specification.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include a pharmaceutical composition comprising an ingredient (B) without limitation.

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the chemical arts is high, it would require undue experimentation of one of ordinary skill in the art to resolve any ingredient (B) without limitation. It would also require undue experimentation to obtain any ingredient (B) having acetylcholine esterase inhibitory activity without limitation. The only guidance present in the instant specification is the exemplary compounds on pages 17-18 of the specification. There is no guidance or working examples present for constitutional any ingredient (B) without limitation. Therefore, the claims lack enablement for all ingredient (B) without limitation. Incorporation of the limitation of the any ingredient (B) (i.e., compound B1 or B2) into claims 1-8 respectively would overcome this rejection.

7. Claims 3 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for treating Alzheimer's disease, does not reasonably provide enablement for the pharmaceutical composition for improving cerebral function without limitation, see claim 1. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a pharmaceutical composition pharmaceutical composition for improving cerebral function without limitation, see claims 3 and 7-8.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the compound Tacrine as acetylcholine esterase inhibitors for treating Alzheimer's disease, pleases visit the Web site at http://en.wikipedia.org/wiki/Tacrine.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the exemplary compounds of the ingredient (B) on pages 17-18 of the specification.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include a pharmaceutical composition for improving cerebral function without limitation.

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the chemical arts is high, it would require undue experimentation of one of ordinary skill in the art to resolve any pharmaceutical compositions for improving cerebral function without limitation. It would also require undue experimentation to obtain any pharmaceutical compositions for improving cerebral function without limitation. The only guidance present in the instant specification is the exemplary compounds on pages 17-18 of the specification. There is no guidance or working examples present for constitutional any pharmaceutical

compositions for improving cerebral function without limitation. Therefore, the claims lack enablement for any pharmaceutical compositions for improving cerebral function without limitation. Incorporation of the limitation of "improving cerebral function" (i.e., Alzheimer's disease) into claims 3 and 7-8 respectively would overcome this rejection.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1-8, recites limitation "an compound having an acetylcholine esterase inhibitory activity", is indefinite and ambiguous, see claim 1. It is unclear what the "an compound having an acetylcholine esterase inhibitory activity" is. The range of "an compound having an acetylcholine esterase inhibitory activity" of claim 1-8 is from compounds of compound B1 or any compounds having inhibitory activity against acetylcholine esterase. Such breath in view of the limited exemplification and the lack of scope of subject matter resulted from a search of the prior art indicated that the "scope" of claim 1-8 can not be ascertained. In view of the high degree of unpredictability of the chemical art and "an compound having an acetylcholine esterase inhibitory activity" must be made available at the time the invention was made, i.e., filing of application, the broad scope can not be supplemented with future discovery of new "an compound

having an acetylcholine esterase inhibitory activity". It is recommended that "an compound having an acetylcholine esterase inhibitory activity" be limited to the specific disclosure of compound (I.e., compound B1 or B2), see pages 17-18 of the specification.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

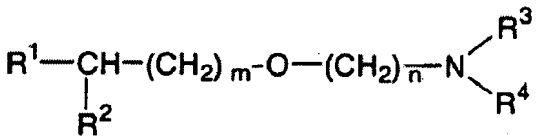
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being obvious over Mealy et al. publication, Drugs of the future, 2002, 27(9): 879-915.

Applicants claim a pharmaceutical composition comprising ingredients (A), wherein the ingredients (A) is compounds of the formula, i.e.,



, and ingredient (B) having acetylcholine esterase inhibitory activity (i.e., . Applicants' pharmaceutical composition is used for treating Alzheimer's disease or for improving cerebral function.

Determination of the scope and content of the prior art (MPEP §2141.01)

Mealy et al. disclose a number of compounds fro treating Alzheimer's disease, see drugs in the Table on page 880-882. Especially, Deonepezil, T-588, Rivastigmine, Galanthamine, Zanapezil, and Pheneserine have been specifically exemplified, see page 883, 904, or 910 respectively. A treatment using a pharmaceutical combination containing a drug treating Alzheimer's disease Memantine and another cholinesterase

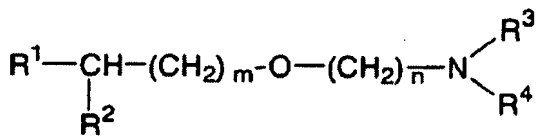
inhibitor Donepezil has been particularly disclosed, see Table 1 on page 884. The instant compound T-588 is known for treating Alzheimer's disease, see page 910.

Determination of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and Mealy et al. is that the ingredient (A) (i.e., agents for treating Alzheimer's disease) of the instant invention is a compound of formula (I) and the ingredient (B) (i.e., agents of acetylcholinesterase inhibitor) is selected from Donepezil (compound B1), Tacrine (compound B2), Rivastigmine, Galanthamine, Zanapezil or Phenserine, while Mealy et al. is T-588 (i.e., ingredient (A)) or Deonepezil, Rivastigmine, Galanthamine, Zanapezil, and Pheneserine (i.e., ingredient (B)). Mealy et al. teachings or pharmaceutical composition inherently overlap with the instant invention.

Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the instant claims 1-8 and prima facie obvious **because** one would be motivated to employ the compounds and their salts of Mealy et al. inherently teachings to obtain the instant pharmaceutical compositions, comprising ingredients (A) (i.e., T-588) of the formula, i.e.,



, and ingredient (B) having acetylcholine

esterase inhibitory activity (i.e., Deonepezil, Rivastigmine, Galanthamine, Zanapezil, and Pheneserine). Dependent claims 2-8 are also rejected along with claim 1 under 35 U.S.C. 103(a).

The motivation to obtain the claimed compounds/compositions derives from known Mealy et al. compounds/compositions would possess similar activities (i.e., agents for pharmaceutical composition for treating Alzheimer's disease) to that which is claimed in the reference.

Claim Objections

11. Claims 1-8 are objected to as containing non-elected subject matter, i.e., heterocyclic group, benzofuranyl group, pyrrolidine, piperazine, or piperidine ring, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on pages 2-3 *supra*.

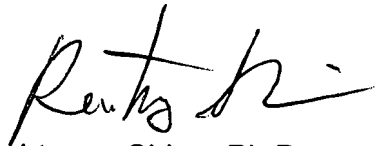
12. Since claims 4 and 8 are drawn to a method of preparation of a pharmaceutical composition, amendment of claims 4 and 8 as a method of preparing a pharmaceutical composition would obviate the objection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Rei-tsang Shiao, Ph.D.
Patent Examiner
Art Unit 1626

May 21, 2007